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Comparative Neurohormonal Responses in Patients With Preserved and Impaired Left Ventricular Ejection Fraction: Results of the Studies of Left Ventricular Dysfunction (SOLVD) Registry

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Objectives. The aim of this study was to determine the differences in neurohumoral responses between patients with pulmonary congestion with and without impaired left ventricular ejection fraction.

Background. Previous studies have established the presence of neurohumoral activation in patients with congestive heart failure. It is not known whether the activation of these neurohumoral mechanisms is related to the impairment in systolic contractility.

Methods. The 898 patients recruited into the Studies of Left Ventricular Dysfunction (SOLVD) Registry substudy were examined to identify those patients with pulmonary congestion on chest X-ray film who had either impaired (≤45%, group I) or preserved (>45%, group II) left ventricular ejection fraction. Plasma norepinephrine, plasma renin activity, arginine vasopressin and atrial natriuretic peptide levels were measured in these two groups of patients and compared with values in matched control subjects.

Results. Distribution of the New York Heart Association symptom classification was the same in the two groups of patients. Compared with control subjects, patients in group II with pulmonary congestion and preserved ejection fraction had no activation of the neurohumoral mechanisms, except for a small but statistically significant increase in arginine vasopressin and plasma renin activity. Compared with patients in group II, those in group I with pulmonary congestion and impaired ejection fraction had significant increases in plasma norepinephrine ($p < 0.002$), plasma renin activity ($p < 0.02$) and atrial natriuretic peptide levels ($p < 0.0007$). When we controlled for baseline differences between groups I and II, the between-group differences in plasma norepinephrine ($p < 0.02$) and atrial natriuretic peptide ($p < 0.002$) remained significant. However, plasma renin activity was not significantly different between groups I and II. When the effects of diuretic agents and angiotensin-converting enzyme inhibitors were adjusted, patients with lower ejection fraction were found to have significantly higher plasma norepinephrine and atrial natriuretic peptide levels.

Conclusions. The results point to the importance of the decrease in left ventricular ejection fraction as one of the mechanisms for activation of neurohormones in patients with heart failure.

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The presence of pulmonary congestion and edema due to elevated left ventricular filling pressures is a well recognized characteristic of patients with congestive heart failure. Although in most patients, congestive heart failure may be due to depressed systolic contractile function, left ventricular diastolic dysfunction can also be the cause of increased ventricular filling pressures (1). Recently, a substantial subset of patients has been identified with symptomatic congestive heart failure in the presence of normal systolic function (2,3). In patients with congestive heart failure, plasma norepinephrine (4,5), plasma atrial natriuretic peptide (6) and plasma renin activity are increased (7). Despite the progress made in understanding the pathophysiology of congestive heart failure, the mechanisms underlying the activation of the neurohumoral systems in patients with heart failure are not well understood. In particular, it is not known whether the impairment of left ventricular systolic function is a

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prerequisite for activation of neurohormonal mechanisms. When cardiac output decreases after myocardial damage, neurohormones are activated to preserve circulatory homeostasis. Therefore, the severity of impairment in systolic function may relate to the degree of neurohumoral activation. In contrast, it may be hypothesized that patients with heart failure and preserved systolic function may not demonstrate an activation of the neurohumoral mechanisms.

The Studies of Left Ventricular Dysfunction (SOLVD) Registry was designed to examine the clinical outcome of patients with a broader spectrum of left ventricular dysfunction (ejection fraction ≤45% or radiologically confirmed diagnosis of congestive heart failure) than that of the main SOLVD trials, which enrolled patients with an ejection fraction ≤35%. Among patients in the SOLVD Registry who presented with congestive heart failure and evidence of pulmonary congestion, we compared neurohormonal levels between patients with a left ventricular ejection fraction ≤45% and an ejection fraction >45%.

Methods

Study design. The SOLVD program was a multicenter program of research into left ventricular dysfunction and congestive heart failure. It included two trials and a registry. The prevention trial showed that enalapril, an angiotensin-converting enzyme inhibitor, prevented the development of symptoms of congestive heart failure in patients who had a left ventricular ejection fraction ≤35% and were not receiving therapy for heart failure (8). The treatment trial demonstrated that enalapril reduced the incidence of death in patients with mild to moderate congestive heart failure (mainly New York Heart Association classes II and III with left ventricular ejection fraction ≤35%) and symptoms of heart failure requiring treatment (9). The SOLVD Registry study was conducted in 18 of the 23 SOLVD centers. Patients with an ejection fraction ≤0.45% or a radiologically confirmed discharge diagnosis of congestive heart failure during the recruitment period (January 1, 1988 to February 28, 1989) were invited to participate in the registry. Patients with nonvalvular congenital heart disease, any noncardiac life-threatening disease, lack of reliable means of follow-up or failure to consent to participate were excluded. Baseline information that was abstracted from the charts included the following: demographic data, clinical history, physical examination, ejection fraction, etiology of the disease, chest X-ray findings, medication used, electrocardiogram (ECG) and laboratory results.

From the 6,273 patients recruited into the SOLVD Registry, a subgroup of 898 patients were randomly selected after stratification by etiology (36% of patients with ischemic or hypertensive heart disease and 100% of patients with other etiologies). Details of the registry methods and sampling procedure have been previously published (10). In this subgroup, a detailed history was obtained and physical examination, a two-dimensional echocardiogram including ejection fraction, chest X-ray film, 12-lead ECG and walk test were done. Of these 898 patients, a subset of 41 patients was identified retrospectively as having an ejection fraction >45% and pulmonary congestion on chest X-ray film, whereas another 89 patients were identified as having both pulmonary edema on chest X-ray film and an ejection fraction ≤45%. The present analyses were conducted on this sample. In addition, neurohormonal measurements were made on 56 age-matched control subjects with no history or physical findings of heart disease or hypertension. None were taking medications known to influence neurohormones. Men composed 70% of the control group and the average age was 56 ± 12 years (range 37 to 80).

The study protocol was approved by the local hospital review boards and the National Institutes of Health. All control subjects and patients provided written informed consent to participate in the study.

Neurohormone measurements. An intravenous cannula was inserted in an arm vein and flushed with heparinized saline solution. Patients were then allowed to rest supine in a quiet room for 30 min. Five ml of blood was placed into a prechilled tube containing reduced glutathione and ethylenebis(oxyethylene-nitrilo) tetraacetic acid (EGTA) for measurement of plasma norepinephrine. The sample was centrifuged within 1 h at 4°C at 2,500 rpm for 12 min. Plasma was stored at ≤−20°C. Five ml each for plasma renin activity, arginine vasopressin and atrial natriuretic peptide analysis was placed into prechilled evacuated tubes containing sodium ethylenediaminetetraacetic acid (EDTA). The three tubes were mixed gently and placed on ice and centrifuged within 1 h of collection at 4°C at 2,500 rpm for 12 min. The supernatant plasma was stored as for plasma norepinephrine.

Neurohormone assays. Samples from all the centers were shipped on dry ice for analysis to the SOLVD neurohormone core laboratory at the University of Texas Medical School at Houston. Plasma norepinephrine was measured by a radioenzymatic method (11). Plasma renin activity was measured using the modified radioimmunoassay technique of Sealey and Laragh (12). Plasma arginine vasopressin and atrial natriuretic peptide were measured by a simplified radioimmunoassay using commercially available antibodies (13). All samples were analyzed in a blinded manner without knowledge of the patients' characteristics.

Sensitivity and reproducibility of assays. The radioenzymatic assay for plasma norepinephrine has a sensitivity of 1 pg/ml with a sample to blank radioactivity count ratio of >2 and an interassay coefficient of variation of 6.1% (calculated from 20 different assays done consecutively on 20 different days). The radioimmunoassay for plasma renin activity was dependent on the sensitivity of the antibody used in the assay that could reliably detect 2 pg of angiotensin I (sample to blank ratio 2). This assay could detect very low plasma renin activity (0.1 ng/ml per h). The interassay coefficient of variation for plasma renin activity was 12.6%. The radioimmunoassay for atrial natriuretic peptide has a sensitivity of 2 pg/ml, and the sensitivity for arginine vaso-

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pressin is 0.22 pg/ml. The interassay coefficients of variation for atrial natriuretic peptide and arginine vasopressin were 13.7% and 11.6%, respectively. In addition, previously assayed quality control samples of plasma norepinephrine were mailed every 2 months from the core laboratory to the SOLVD study centers. These samples were stored and returned in the same way as the patient samples. On return, these quality control samples were reanalyzed to assess the stability of samples during storage and transportation. There were no significant differences in the plasma norepinephrine values (278 ± 28 vs. 269 ± 32 pg/ml) in 123 samples analyzed in this manner.

Left ventricular dimensions and ejection fraction were measured by two-dimensional echocardiography using the multiple diameter method (14). The left ventricular dimensions were measured below the tip of the mitral leaflets at end-diastole (onset of the QRS complex) and at end-systole (one frame before mitral valve opening). The average variability in ejection fraction measurement was <3%. Left atrial dimensions were taken at the point of maximal anterior root motion in the same plane as the aortic root. All measurements were made by the echocardiography core laboratory at Baylor College of Medicine in Houston.

Statistical methods. Between-group differences were evaluated by chi-square tests (categoric variables) or Wilcoxon two-sample tests (continuous variables). Because the neurohormonal data were not normally distributed, nonparametric methods were used for simple correlations (Spearman rho) and between group comparisons (Wilcoxon two-sample test) (15). Covariate analysis was conducted separately for each covariate, with the group (left ventricular ejection fraction ≤45% vs. >45%) and the covariate as independent variables and the natural logarithm of the neurohormone values as the dependent variable. Log transformation (16) was used because it improved the distribution characteristics of the data.

Table 1. Patient Characteristics

	Group I* (n = 89)	Group II† (n = 41)	p Value
Age (yr)	62 ± 13	66 ± 15	NS
Male	75	39	< 0.0009
Race			
White	69	83	NS
Black	29	17	
Other	2	0	
Etiology (%)			NS
Ischemic heart disease	31	27	
Idiopathic cardiomyopathy	33	22	
Hypertensive heart disease	13	15	
Specific	12	15	
Other	10	22	
Systolic BP (mm Hg)	128 ± 19	132 ± 17	NS
Diastolic BP (mm Hg)	79 ± 13	76 ± 9	
NYHA class			
I	24	27	NS
II	46	46	
III	21	20	
IV	4	7	
Elevated JVP	23	13	NS
S_3 gallop	33	3	0.001
CT ratio	0.57 ± 0.06	0.56 ± 0.09	NS
Diuretic use	90	75	0.05
Digitalis use	74	41	0.001
Beta-blocker use	6	8	NS
ACE inhibitor use	58	35	0.04
Serum sodium (mEq/liter)	138 ± 4.7	138 ± 4.0	NS
Serum potassium (mEq/liter)	4.2 ± 0.5	4.3 ± 0.5	NS
Blood urea nitrogen (mg/dl)	23.3 ± 10.1	25.3 ± 12.8	NS
Serum creatinine (mg/dl)	1.3 ± 0.3	1.1 ± 0.4	0.02

*Group I = patients with left ventricular ejection fraction (EF) ≤45% with pulmonary congestion on chest X-ray film. †Group II = patients with left ventricular EF >45% with pulmonary congestion on chest X-ray film. Values are expressed as mean value ± SD or percent of patients. ACE = angiotensin-converting enzyme; BP = blood pressure; CT = cardiothoracic; JVP = jugular venous pressure; NYHA class = New York Heart Association functional class; S_3 gallop = third heart sound.

Results

Clinical characteristics. The demographic characteristics of patients entering these two study groups are given in Table 1. There were no significant differences between the groups with respect to age or race. However, men comprised 75% of the participants in group I, whereas women comprised 61% of the patients in group II ($p < 0.0009$). The underlying incidence of ischemic heart disease was similar between the two groups. The distribution of the New York Heart Association symptom class was the same between the two groups of patients (Table 1). Physical findings were also similar for patients in groups I and II with respect to presence or absence of peripheral edema, elevated jugular venous pressure and history of breathlessness on exertion. However, only 3% of patients in group II had an S_3 gallop, whereas in group I it was present in 33% ($p < 0.001$). Cardiomegaly was present in both groups of patients and did not differ significantly between groups. The use of diuretic agents, digitalis and angiotensin-converting enzyme inhibitors was also significantly higher in patients in group I (Table 1). Probably secondary to increased use of diuretic agents or angiotensin-converting enzyme inhibitors in this group of patients, serum creatinine was also significantly increased compared with the value in group II (Table 1).

We also searched for evidence of alteration in diastolic function in these two groups of patients. In both patient groups, left atrial dimensions were increased (group I median 4.3 cm, interquartile range 3.9 to 4.8 cm; group II median 4.1 cm, interquartile range 3.4 to 4.6 cm; p = NS between groups). In a smaller number of patients in each group, Doppler echocardiographic cardiac measurements of mitral valve E/A ratios were made. In both groups of patients, the values were decreased below normal (group I median 1.15, interquartile range 0.70 to 2.48; group II

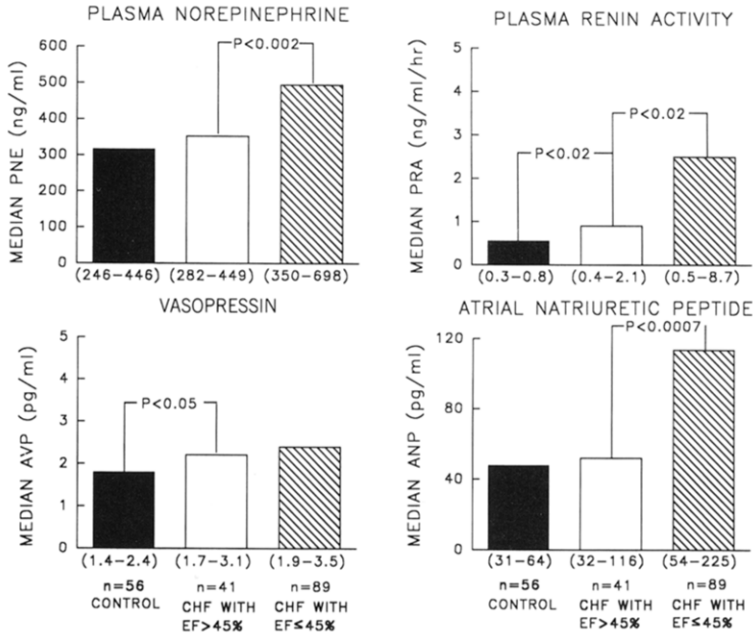

Figure 1. Graphs showing significant increases in plasma norepinephrine (PNE), plasma renin activity (PRA), plasma arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) levels in 56 control subjects, 41 patients with pulmonary congestion on chest X-ray film and left ventricular ejection fraction (EF) >45% (group II) and 89 patients with pulmonary congestion and an ejection fraction ≤45% (group I). Median values and interquartile ranges (25% to 75%) are shown for the four neurohormones. CHF = congestive heart failure.

median 0.82, interquartile range 0.66 to 1.82; p = NS between groups).

Plasma neurohormones. When compared with values in control subjects, the median values and the interquartile ranges for all four neurohormones were significantly higher in patients in group I (plasma norepinephrine: control subjects 316 [range 246 to 446] vs. 490 [range 350 to 698] pg/ml, $p < 0.0001$; plasma renin activity 0.6 [range 0.3 to 0.8] vs. 2.5 [range 0.5 to 8.7] ng/ml per h, $p < 0.0001$; atrial natriuretic peptide 48 [range 31 to 64] vs. 114 [range 54 to 225] pg/ml, $p < 0.0001$ and arginine vasopressin 1.8 [range 1.4 to 2.4] vs. 2.4 [range 1.9 to 3.5] pg/ml, $p < 0.0001$, respectively) (Fig. 1). However, when control subjects were compared with the patients in group II, only arginine vasopressin and plasma renin activity were significantly higher in group II (arginine vasopressin: control subjects 1.8 [range 1.4 to 2.4] vs. 2.2 [range 1.7 to 3.1] pg/ml, $p < 0.02$ and plasma renin activity 0.55 [range 0.3 to 0.9] vs. 0.9 [range 0.4 to 2.1], $p < 0.02$, respectively) (Fig. 1). Compared with patients in group II, those in group I with pulmonary congestion and impaired ejection fraction had significant increases in plasma norepinephrine ($p < 0.002$), plasma renin activity ($p < 0.02$) and atrial natriuretic peptide ($p < 0.007$) levels. Because of baseline imbalances in gender between groups I and II, we also examined the differences in neurohormones after controlling for this difference. The between-group differences in plasma norepinephrine ($p < 0.02$) and atrial natriuretic peptide ($p < 0.002$) remained significant, whereas the differences in plasma renin activity were reduced to nonsignificance. There were also no differences in the history of hypertension or mean systolic and diastolic blood pressures between these two groups of patients (Table 1).

In a previous study (17), we demonstrated that the activation of neurohumoral mechanisms was correlated to a decrease in left ventricular ejection fraction. Therefore, we examined whether such a correlation existed in patients in group I. Table 2 and Figure 2 show the correlation between ejection fraction measured in the patients by two-dimensional echocardiogram and the various neurohormones for the patients with ejection fraction ≤45% and pulmonary congestion on chest X-ray film. The increase in plasma neurohormones, with the exception of arginine vasopressin, correlated significantly with a decrease in ejection fraction in these patients. In contrast, no such correlation was present between a change in ejection fraction and neurohormones in patients with ejection fraction >45% and pulmonary congestion (group II). Because patients with a low ejection fraction are more likely to be receiving larger doses of diuretic agents or angiotensin-converting enzyme inhibitors, or both, which can alter plasma neurohormonal levels, in separate analyses we adjusted for the effect of concomitant diuretic or angiotensin-converting enzyme inhibitor therapy, or both. Even after adjusting for the differences in drug treatment, plasma norepinephrine and atrial natriuretic peptide were significantly elevated in patients in group I, compared with values in patients in group II (plasma norepinephrine $p < 0.02$, atrial natriuretic peptide $p < 0.0003$). In group I patients, the relation between ejection fraction and neurohormones remained statistically significant even after adjusting for the effect of drug therapy with angiotensin-converting enzyme inhibitors, digitalis, diuretic agents and beta-adrenergic blockers (plasma norepinephrine $p < 0.05$, plasma renin activity $p < 0.04$ and atrial natriuretic peptide $p < 0.003$).

We also examined the relation between neurohormones and left atrial size and left ventricular systolic and diastolic dimensions. In patients with both left ventricular ejection fraction ≤45% and pulmonary congestion on chest X-ray

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Table 2. Correlation of Plasma Neurohormones With Ejection Fraction and Left Ventricular Dimensions in Patients With Left Ventricular Dysfunction and Congestive Heart Failure

	PNE		PRA		AVP		ANP	
	Group I*	Group II†	Group I	Group II	Group I*	Group II	Group I	Group II
Ejection fraction (%)								
No.	88	38	87	39	73	34	72	34
rho	−0.27	0.24	−0.25	−0.05	−0.03	0.14	−0.45	0.10
p value	0.02	NS	0.02	NS	NS	NS	0.0001	NS
LV systolic dimension (cm)								
No.	88	38	87	39	73	34	72	34
rho	0.17	−0.15	0.36	0.09	0.12	−0.18	0.33	0.01
p value	NS	NS	0.0007	NS	NS	NS	0.005	NS
LV diastolic dimension (cm)								
No.	88	38	87	39	73	34	72	34
rho	0.08	−0.12	0.37	0.17	0.16	−0.06	0.20	0.10
p value	NS	NS	0.0005	NS	NS	NS	NS	NS
LA dimension (cm)								
No.	88	37	87	38	73	33	72	33
rho	0.11	0.37	−0.04	−0.19	0.26	−0.13	0.37	0.64
p value	NS	0.03	NS	NS	0.03	NS	0.002	0.0001
CT ratio								
No.	72	29	72	30	61	26	60	26
rho	0.08	0.29	−0.12	−0.09	−0.09	0.02	0.37	0.26
p value	NS	NS	NS	NS	NS	NS	0.004	NS

*Group I = patients with left ventricular ejection fraction ≤45% with pulmonary congestion on chest X-ray film. †Group II = patients with left ventricular ejection fraction >45% with pulmonary congestion on chest X-ray film. ANP = atrial natriuretic peptide; AVP = arginine vasopressin; CT = cardiothoracic; LA = left atrial; LV = left ventricular; PNE = plasma norepinephrine; PRA = plasma renin activity; rho = Spearman rank order correlation coefficient.

film, plasma renin activity and atrial natriuretic peptide were statistically and significantly correlated with either left atrial size or left ventricular systolic and diastolic dimensions (Table 2). However, the best correlation was observed between plasma atrial natriuretic peptide levels and left atrial size (rho 0.37, $p < 0.002$) and left ventricular systolic volume (rho 0.33, $p < 0.005$). This is consistent with the observation that of the four neurohormones examined, atrial natriuretic peptide showed the best correlation with cardiothoracic ratio on chest X-ray film (rho 0.37, $p < 0.004$). Although in patients with pulmonary vascular congestion and ejection fraction >45% (group II), atrial natriuretic peptide levels

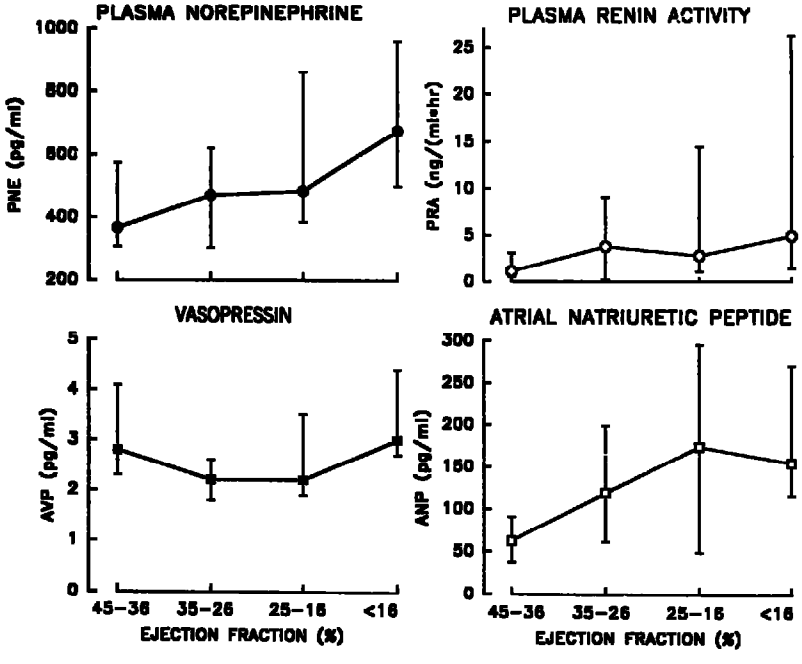

Figure 2. Relation between left ventricular ejection fraction and the four neurohormones studied in patients with a left ventricular ejection fraction ≤45% and pulmonary congestion on chest X-ray film (group I). Patients were classified into those with an ejection fraction of 36% to 45% (n = 21), 26% to 35% (n = 29), 16% to 25% (n = 32) and <16% (n = 7). Plasma norepinephrine (PNE), plasma renin activity (PRA) and atrial natriuretic peptide (ANP) increase with increasing left ventricular dysfunction. In contrast, arginine vasopressin (AVP) does not change. Median value and the interquartile ranges (25% to 75%) are shown for the four neurohormones.

were not significantly elevated above those in the control group, a significant correlation was found between left atrial size and atrial natriuretic peptide levels (rho 0.64, $p < 0.0001$). This finding strongly suggests that an increase in atrial natriuretic peptide levels can develop without the presence of systolic dysfunction and correlates with the increase in left atrial dimension.

Discussion

Congestive heart failure is a clinical syndrome associated with a broad spectrum of alteration in myocardial function with varying components of systolic and diastolic impairment. Neurohumoral activation is an important manifestation in patients with congestive heart failure. Previous studies examining the neurohormonal alterations have focused mainly on patients with severe impairment in systolic contractility. It is not clear whether patients with symptoms of congestive heart failure and preserved systolic function have similar alterations in neurohumoral mechanisms. In our study, we examined patients from the SOLVD Registry, where patients were not recruited on the basis of eligibility for a trial of patients with congestive heart failure and are thus more representative of the general population of patients with left ventricular dysfunction. These results show that compared with age-matched control subjects, patients with pulmonary vascular congestion and preserved systolic function (ejection fraction >45%) have no increase in neurohormones except for arginine vasopressin and plasma renin activity. In contrast, patients with pulmonary vascular congestion and impaired systolic function (ejection fraction ≤45%) have a significant increase in all four neurohormones studied.

The increase in three neurohormones (plasma norepinephrine, plasma renin activity and atrial natriuretic peptide) was statistically and significantly correlated with left ventricular ejection fraction in patients with systolic dysfunction, with atrial natriuretic peptide showing the best correlation. This relation was demonstrable even after adjusting for the effect of drug therapy on various neurohormones. The absolute plasma norepinephrine level in patients with congestive heart failure is influenced by alterations in neuronal uptake, clearance and metabolism of norepinephrine released from the sympathetic nerve endings. However, the measurement of efferent sympathetic nerve traffic by intraneuronal recording in the peroneal nerve in patients with congestive heart failure demonstrates evidence of increased central sympathetic outflow and elevated plasma norepinephrine levels in these patients (18). If the stimulus for activation of the sympathetic nervous system is poor pump function, then it is not unreasonable to expect a correlation between left ventricular ejection fraction and plasma norepinephrine levels. We found a relatively weak correlation between plasma norepinephrine, which has also been observed in other clinical studies (19,20) in patients with moderate to severe symptoms of heart failure. There was also a weak correlation between ejection fraction and plasma renin activity. This relation with ejection fraction persisted despite adjusting for the effect of concomitant therapy with diuretic agents and angiotensin-converting enzyme inhibitors. Although several studies have reported the stimulation of the renin-angiotensin system in congestive heart failure, there is no agreement on the frequency or amplitude of this stimulation in patients with varying degrees of congestive heart failure. Dzau et al. (21) reported that the system is markedly activated during acute decompensation but near normal when patients have recovered from the acute episode. Therefore, the clinical status of the patient with congestive heart failure (compensated or decompensated) will affect the measured plasma renin activity levels. Further, diuretic use and sodium restriction affect the renin-angiotensin system and increase plasma renin activity levels (22,23). However, Anand et al. (24) showed that five of eight patients with advanced untreated chronic congestive heart failure with salt and water retention had elevated plasma renin activity levels. Similar findings have been reported by Brown et al. (25) in untreated patients with congestive heart failure. These data suggest that depending on the cohort of patients investigated, the clinical severity of congestive heart failure involved and the medications used, plasma renin activity levels can vary significantly.

Of all the neurohormones, atrial natriuretic peptide showed the strongest correlation with ejection fraction. Atrial natriuretic peptide is synthesized in the myocardium and released mainly in response to increased atrial stretching (26). Plasma atrial natriuretic peptide levels increase with increased atrial pressures and atrial stretch in patients with worsening failure (27,28). Hara et al. (29) found atrial natriuretic peptide levels in plasma to correlate inversely with the level of ejection fraction and directly with the severity of congestive heart failure. Similarly, Rouleau et al. (30) found an inverse correlation between atrial natriuretic peptide and cardiac index. In this study, atrial natriuretic peptide correlated with left atrial size and the strongest correlation was found in patients with preserved systolic function. This finding is in keeping with the suggestion that the increase in atrial natriuretic peptide levels develops early as a result of distension of the left atrium and tends to correlate with left atrial dimension. However, in contrast to patients with predominantly diastolic dysfunction who experience mainly transient episodes of an increase in left ventricular end-diastolic pressure, patients with impaired systolic contractility tend to have a sustained increase in left ventricular end-diastolic pressure. This sustained increase may result in chronic stretching and alteration in left atrial compliance, which may be one of the explanations for the less striking correlation between atrial natriuretic peptide levels and left atrial dimension in patients with impaired systolic left ventricular function (31).

Plasma arginine vasopressin levels showed a significant increase in both groups of patients compared with the level in normal subjects. This may be due to the increased release

of arginine vasopressin that occurs with the development of pulmonary congestion with resulting levels that may not increase further with impairment in systolic contractility. Although a previous study (32) demonstrated an increase in arginine vasopressin levels in direct proportion to hemodynamic and clinical severity of heart failure, the present study failed to show a strong relation between arginine vasopressin and ejection fraction. In congestive heart failure, the mechanism for the release of arginine vasopressin is unclear, but it is believed to be due to nonosmotic causes (33,34). Plasma arginine vasopressin levels are frequently increased in parallel to an increase in plasma renin activity (35) as a result of compromised end-organ perfusion. Furthermore, baroreceptor stimulation is a common stimulus for release of both arginine vasopressin and plasma renin activity, and increases in angiotensin II may directly stimulate the hypophysical production of arginine vasopressin (36). Although we observed an increase in plasma renin activity with increasing left ventricular dysfunction, there was no change in arginine vasopressin levels. This suggests that release of arginine vasopressin is probably not a primary mechanism for increasing the peripheral resistance in most patients with congestive heart failure and the nonosmotic mechanisms of arginine vasopressin release may induce only a limited increase in plasma arginine vasopressin levels.

Conclusion. Plasma neurohormonal levels in patients with congestive heart failure are dependent on a complex interplay among symptoms, medications used and the degree of left ventricular dysfunction. In the absence of left ventricular dysfunction, neurohumoral mechanisms are not activated except for a minimal increase in the level of arginine vasopressin and plasma renin activity. With the onset of systolic left ventricular dysfunction, activation of plasma norepinephrine and atrial natriuretic peptide develops in these patients. This study from the SOLVD Registry broadens our understanding of neurohumoral activation that was previously obtained from the original SOLVD neurohormonal study (17) and its applicability to patients with pulmonary congestion and with or without systolic dysfunction of the left ventricle.

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